Stevia: It's Not Just About Calories

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Abstract: *Objective*: Although stevia leaf extract is an accepted sugar substitute that can contribute to improved caloric management and weight control, it also may enhance other aspects of human health. The effectiveness and safety of stevia leaf extract in these additional roles was evaluated. *Methods*: A detailed literature review was conducted and summarized. *Results*: An extract of the leaf of the herb, *Stevia rebaudiana* Bertoni ("stevia") is a natural, sweet-tasting, noncaloric substance and does not produce unhealthy side effects. In addition, the inclusion of stevia leaf extracts in the diet has been associated with antihyperglycemic, insulinotropic, glucagonostatic, hypotensive, anticariogenic, antiviral, antimicrobial, anti-inflammatory, immunostimulatory and chemopreventative responses. *Conclusion*: Stevia leaf extracts and their constituent phytonutrients promote caloric balance and can be beneficial components of a healthy dietary lifestyle.

Keywords: Stevia, glucose, blood pressure, sweetener, immunostimulation.

INTRODUCTION

The overconsumption of refined sugars, especially sucrose, promotes inappropriate positive caloric balance, loss of body weight control, excessive weight gain and obesity [1-3]. In addition, this dietary habit contributes to the etiologies of type 2 diabetes [2-9], cancer [10-22], dental caries [23-25], candidiasis [26-28] and inflammatory bowel disease [29-33]. In a society in which the challenge of maintaining a healthy caloric balance is overwhelming to over half of the population, noncaloric sweeteners may offer some hope to those who desire to avoid the debilitating diseases associated with excessive sugar consumption [34]. Unfortunately, synthetic noncaloric sweeteners are associated with increased likelihood of increased caloric intake and inability to achieve or maintain healthy body weight and provide no other health benefits [35,36].

In contrast, a considerable body of scientific evidence supports the effectiveness and safety in human health promotion of extracts of the leaf of the "sweet herb" stevia (*Stevia rebaudiana* Bertoni), a potent nonsynthetic noncaloric sweetener [37-41]. These extracts contain several sweet-tasting diterpenoid glycosides of the aglycone, steviol, including stevioside (300-fold sweeter tasting than sucrose), rebaudioside A (reb A; 250- to 450-fold sweeter), reb B (300- to 350-fold sweeter), reb C (50- to 120-fold sweeter), reb D (250- to 450-fold sweeter), reb E (150- to 300-fold sweeter), steviobioside (100- to 125-fold sweeter), dulcoside A (50- to 120-fold sweeter), isosteviol and dihydroisosteviol [42]. The relative sweetness of these diterpenoid glycosides appears to reflect differences in the carbohydrate residues at the 13 and 19 carbons of the common steviol aglycone backbone [42]. Procedures for the extraction and purification of these compounds and a review of their pharmacokinetics are provided by Chatsudthipong and Muanprasat [42].

A perennial herb native to Paraguay and Brazil and used widely today in Asia and South America, stevia has gained recent attention by numerous food and beverage multinational enterprises [43]. Japan began marketing stevioside as a sweetener in the 1970s, when chemical sweeteners were banned and replaced with stevia [44]. Since then, cultivation of the plant has expanded to other countries including China, Malaysia, Singapore, South Korea, Taiwan, Thailand, Paraguay, Brazil, the U.S., Canada and Europe [42,44].

Stevia extract and stevioside are officially approved as food additives in Brazil, Korea and Japan [42]. Europe is key among future markets for Stevia. In 2006, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) announced a temporary accepted daily intake (ADI) of stevioside of up to 5.0mg/kg body weight (BW) [45]. In September 2009, the French Government (*via* interministerial decree) became the first government in the European Union (EU) to approve Stevia extracts consisting of at least 97% Rebaudioside A (Reb A) as food and beverage sweeteners. Following the recent U.S. FDA recognition of high purity Reb A from key producers as "Generally Recognized as Safe (GRAS)" [46], the global market is now looking forward to approval from the European Food Safety Association (EFSA).

METHODS

A set of comprehensive literature searches were conducted in order to identify the relevant English-language publicly available scientific literature. The U.S. National Library of Medicine PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) and TOXNET Toxicology Data Network (http://toxnet.nlm.nih.gov/) databases, along with secondary sources cited by primary sources were examined. There were no limits set on the publication dates of relevant literature.

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BEYOND OBESITY – HEALTH RISKS ASSOCIATED WITH OVERCONSUMPTION OF SUCROSE

Excess Body Weight, Type 2 Diabetes and the Metabolic Syndrome

Overweight and obese individuals are subject to societal stigmatization and are at increased risk for deleterious health conditions, including type 2 diabetes, cardiovascular diseases, hypertension, osteoarthritis, and some cancers [47,48]. Overweight and obesity also increase health care costs and mortality rates [47-50].

Excessive body weight, type 2 diabetes and the metabolic syndrome have reached epidemic proportions in the United States and many parts of the world [4,51,52]. The term "metabolic syndrome" describes the concurrent presence of abdominal obesity, insulin resistance, dyslipidemia and hypertension and may be associated with other comorbidities, including the prothrombotic state, elevated systemic inflammation, nonalcoholic fatty liver disease and reproductive disorders [53,54]. It is likely that concomitant insulin resistance and abdominal obesity are central components in the development of the metabolic syndrome [53,55] and are strong contributors to the association between the metabolic syndrome and premature morbidity and mortality [56,57]. For example, among adults, the presence of the metabolic syndrome is associated with an approximate doubling of the risk for cardiovascular disease and a 5-fold increased risk for type 2 diabetes mellitus [53,54].

Emerging evidence reveals that the symptoms of the metabolic syndrome are not merely manifestations of "getting older" but instead overlay a predisposing behavioral, biochemical and physiological milieu that often becomes established during childhood [58,59]. In 2005-2006, approximately 16% of US school children were obese ($\geq 95^{th}$ percentile according to CDC) and another 16% were overweight (85^{th} – 94^{th} percentile) [60]. Obese children are more likely to exhibit hyperlipidemia, hypertension and insulin resistance [61] and to suffer from atherosclerosis, obesity and premature death in adulthood [62].

This epidemic of obesity among both children and adults can be traced to a combination of increased routine caloric intake from simple sugars and reduced physical activity [1,63,64]. One notable contributor to the upsurge in simple sugar intake has been the substantial increase in the amount of dietary fructose consumed in the forms of sucrose and high fructose corn syrup, particularly as sweetened beverages [64-66]. Fructose now supplies 10% of the total daily caloric intake in the U.S. (up from 8% twenty years earlier) [67] and the percentage of total daily caloric intake obtained from beverages has doubled since 1965 [66]. Although sugar intake from beverages is not inherently "fattening," sucrose and fructose in beverages promote weight gain and other metabolic disorders through their impact on daily caloric intake [68-70].

Sugar- and high-fructose corn syrup-sweetened soft drink consumption is an etiologic factor in the establishment of the metabolic syndrome. Among children and adolescents, the average daily consumption of such sweetened soft drinks increases with age [71], body weight is positively correlated with daily sweetened soda consumption [72] and excess sugar consumption during childhood is linked to loss of glucoregulation and the development of obesity [73-75]. Persistent sucrose overconsumption is highly correlated with weight gain, percent body fat and increased risk for the development of cardiovascular disease and type 2 diabetes in adulthood [4,6-8,76]. For example, data obtained during the 2005 New York City Community Health Survey suggest that the habitual consumption of 2 sugar- or high-fructose corn syrup-sweetened beverages daily increases body mass index by about 1.5 units [77]. Data from the 24-year prospective Nurses' Health Study indicate that a 35% increase in the risk for developing coronary heart disease accompanies the long-term consumption of 2 or more sugar- or high-fructose corn syrup-sweetened beverages daily [78]. In the prospective Framingham Heart Study, the chronic daily consumption of a single sugar- or high-fructose corn syrup-sweetened beverage increased the odds of becoming obese by 30%, the odds of experiencing impaired glucose tolerance by 25% and the odds of developing the symptom set of the metabolic syndrome by 50% [9]. In the prospective Nurses' Health Study II, the routine daily consumption of a single sugar- or high-fructose corn syrup-sweetened soft drink nearly doubled the risk for developing type 2 diabetes [79]. In a 6-year prospective study of 44,000 African-American women, the risk for developing type 2 diabetes was increased 24% by the daily consumption of 2 or more sugar- or high-fructose corn syrup-sweetened beverages [80]. In the 9-year prospective Atherosclerosis Risk in Communities Study, a single serving of sugar- or high-fructose corn syrup-sweetened beverages daily increased by 17% the risk of developing the metabolic syndrome [81]. In the cross-sectional Bogalusa Heart Study, greater intakes of sugar-sweetened beverages were associated with the presence of more signs and symptoms of the metabolic syndrome in young adults [82]. The American Heart Association recommends limiting daily sucrose plus fructose intake to no more than 100 calories for women and to no more than 150 calories for men [83].

Obesity and Cancer

The causative or facilitative relationship between obesity and the development of human cancer is undeniable. The results of individual epidemiologic studies in which hundreds of thousands of subjects have been observed for decades, and of a meta-analysis of those studies, demonstrate direct correlations between body mass index (BMI) and the risks of developing cancer of the colon, rectum, prostate, breast, pancreas, esophagus, stomach, gallbladder, liver, kidney, lung, endometrium, uterus, cervix or ovary [16-22, 84]. Consistent with a previous estimate [84], the AICR has estimated that excess body fat (BMI > 25) alone is a direct causative factor in about 10% to 20% of all newly diagnosed cancer cases, and that maintaining BMI < 25 can prevent a high percentage of 7 highly prevalent site-specific solid cancers (Table **1**) [85].

Sucrose and Cancer

In addition to the cancer-predisposing effects of sucrose-induced obesity [1], the results of observational epidemiologic studies have indicated that frequent consumption of sucrose-rich "sweets," particularly desserts, is associated with increased risks for breast cancer [10-13] and pancreatic

Table 1. New Cancers (%) that could be Prevented by Maintaining BMI < 25

Site	USA		UK		Brazil		China	
	Male	Female	Male	Female	Male	Female	Male	Female
Esophagus	32	38	29	33	20	26	14	20
Pancreas	34	25	32	19	25	14	20	10
Gallbladder	11	28	8	21	3	15	2	10
Colorectum	16	3	14	2	8	1	5	1
Breast	---	17	---	16	---	14	---	12
Endometrium	---	49	---	38	---	29	---	18
Kidney	20	28	17	21	10	16	6	10
Total	20	19	18	16	13	13	11	12

cancer [86]. In addition, the routine consumption of large amounts of sucrose increases the frequency of mutations in the colonic mucosa [14] and is associated with increased risk of colon cancer [15]. The World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) have recommended that individuals reduce their risk for developing cancer by avoiding obesity, at least in part by minimizing sugar intakes [87].

Sucrose and Dental Caries

Dietary sugars, particularly sucrose, cause dental caries [23,88,89]. Biochemical, microbiological, animal and human clinical and epidemiological evidence support a causal relationship between sugar consumption and the formation of dental caries [25]. Sucrose, identified as the most cariogenic sugar, forms glucan which promotes firm bacterial adhesion to teeth and limits diffusion of plaque acid and buffers [24]. The risk of caries is related to both the amount and frequency of sucrose intake, with a steep rise in occurrence concurrent with increased sucrose consumption [25]. Increasing the availability of effective and safe replacements for dietary sucrose during critical periods of dental development is vital to long-term public health.

Sucrose and Candidiasis

The adherence of *Candida albicans* determines the ability of yeast to colonize various regions of the host [27]. The adhesion of *C. albicans* and *C. tropicalis* is facilitated in the presence of a high concentration (500 *mM*) of fructose, glucose, maltose, and sucrose, with sucrose exhibiting the greatest promotion of adhesion [26,28]. Limitation of sugar consumption may prevent colonization and infection by various *Candida* organisms.

Sucrose and Inflammatory Bowel Disease

Nutritional and dietary factors contribute to the pathogenesis of the inflammatory bowel diseases, Crohn's disease and ulcerative colitis (UC). Individuals with Crohn's disease have been found to consume above-average amounts of sucrose, refined carbohydrates and ω-6 fatty acids while enjoying only limited fruit and vegetable consumption [29, 90-92]. Population-based case-control studies have observed that the risk of developing Crohn's disease is increased by the daily consumption of 55 g or more of sucrose [30]. A multicenter hospital-based case-control study evaluating the role of dietary factors in the etiology of inflammatory bowel disease discovered that the risk of developing ulcerative colitis or Crohn's disease was positively correlated with the consumption of sugars and sweeteners [31]. A clinic-based case-control study investigating the diets of patients with inflammatory bowel diseases prior to their first diagnosis found that the routine daily consumption of large amounts of sucrose increased the risk for developing inflammatory bowel disease [32]. Since the 1970s, various studies have reported sufficiently high consumption levels of sugar and refined carbohydrates in patients with IBD; they can be considered to be risk factors for CD [32,93,94] and UC [33,94-97]. These findings suggest that the elimination of sucrose from the habitual daily diet may reduce the incidence of inflammatory bowel disease among the general population.

STEVIA

Stevia rebaudiana Bertoni ("stevia") is an herbaceous perennial shrub indigenous to Paraguay and Brazil. Stevioside, the main sweet component in the leaves of this plant, is approximately 300 times sweeter tasting than sucrose [37]. In addition to its natural, noncaloric sweetening properties, extracts of the leaf of stevia have produced beneficial antihypertensive, antihyperglycemic, antioxidant, noncariogenic, chemoprotective, anti-inflammatory, immunomodulatory, and antiviral effects on human health [42].

Stevia is an Effective Noncaloric Sweetener

While white sugar, turbinado, fructose, honey and corn syrup all qualify as natural sweeteners, none are calorie-free, nor are they beneficial dietary components for those who suffer from blood sugar disorders and other conditions. Leaves of the stevia plant contain zero-calorie *ent*-kaurene diterpene glycosides (stevioside and the rebaudiosides) that are not metabolized to produce energy and which taste 300 times sweeter than sucrose [38-41]. In human studies, the measured sweetness of 1 g of crude extract of stevia leaf dissolved in water has ranged from 100 to 150 times that of equivalent concentrations of sucrose [98,99].

Studies conducted assessing sweetness temporal profiles demonstrate changes in perception of sweetness over time. In lab assessments, tested sweeteners exhibit a characteristic Appearance Time (AT) and Extinction Time (ET). In contrast to carbohydrate sweeteners, most high-potency sweetening agents display prolonged ET. This quality has been beneficial in product development, particularly for such innovations as chewing gum, where prolonged sweetness is desirable [100]. In a laboratory comparison, a component of stevia leaf extract (rebiana) exhibited an ET much longer than that for sucrose [100].

STEVIA IS A HEALTHY REPLACEMENT FOR SUCROSE AND HIGH-FRUCTOSE CORN SYRUP

Stevia Contributes to Healthy Glucoregulation

Stevia leaf extract has been used traditionally in the treatment of diabetes [38,39]. Every opportunity to reduce dietary sugar intake is especially beneficial to individuals with diabetes, in whom blood glucose concentrations reflect sugar consumption [101].

Evidence from preclinical studies suggests that stevioside enhances both insulin secretion and insulin sensitivity. The increase in insulin sensitivity induced by the components of stevia leaves may be related to inhibition of hepatic expression of phosphoenolpyruvate carboxykinase (PEPCK) and gluconeogenesis coupled with stimulation of hepatic glycogen synthesis [102,103]. Another component of stevia leaf extract, rebaudioside A, has been shown to stimulate insulin secretion by isolated mouse pancreatic islets [104]. Stevioside also enhances glucose-stimulated insulin secretion but does not affect fasting insulinemia [105,106]. In a 6-week study, stevioside-fed diabetic rats displayed significantly enhanced first-phase insulin responses with concomitant suppression of glucagon secretion and attenuation of blood glucose concentration excursions [107].

Similar beneficial effects appear to occur in humans. In an acute, paired cross-over study, twelve men and women with type 2 diabetes consumed a standard test meal supplemented with either 1 g of stevioside or 1 g of maize starch (control) [108]. Compared to the effects of maize starch, stevioside consumption was associated with significantly greater attenuation of peak postprandial blood glucose concentrations and increase in the insulinogenic index. These findings suggest that replacement of sugars with stevioside-containing stevia leaf extracts can support healthy glucoregulation.

Stevia Contributes to Healthy Blood Pressure Regulation

Studies in rats and dogs have demonstrated that stevioside induces vasorelaxation [109-111]. This effect was tested in a year-long randomized, double-blind, placebo-controlled study of 106 hypertensive subjects who consumed capsules containing either stevioside (750 mg daily) or placebo [112]. Beginning after 3 months and persisting throughout the remaining 9 months of the study, the subjects consuming stevioside exhibited significantly greater decreases in systolic and diastolic blood pressures. No significant adverse effects occurred. In a longer 2-year study, compared to placebo, 1,500 mg of stevioside daily also produced significantly greater decreases in systolic and diastolic blood pressures in subjects with mild hypertension [113].

Stevia Supports the Prevention of Dental Caries

Stevia leaf extract and its major polyphenolic constituents, stevioside and rebaudioside A, are noncariogenic. For example, sucrose solution triggered the development of dental caries in rat pups while stevioside did not [114]. The results of other studies indicate that the major cariogenic organism, *Streptococcus mutans*, experiences growth suppression and secretes less acid when grown on media containing stevioside than when grown on sucrose, glucose or fructose media [115-117].

Stevia is an Effective Antioxidant

Stevia leaf extract exhibits a high degree of antioxidant activity and has been reported to inhibit hydroperoxide formation in sardine oil with a potency greater than that of either DL-α-tocopherol or green tea extract [118,119]. The antioxidant activity of stevia leaf extract has been attributed to the scavenging of free radical electrons and superoxides [118]. Ethanolic extraction of stevia leaves produces three active compounds that, based on results of the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging assay, have been found to exhibit potent antioxidant activity at a concentration of 60 *μMol* [120]. An ethyl acetate extract of a methanolic extract of *Stevia rebaudiana* leaves contains a relatively high concentration of total polyphenols and flavonoids and prevents lipid peroxidation, free radical propagation and DNA strand excision at 0.1 mg/mL [121]. A recent study assessing the *in vitro* potential of ethanolic leaf extract of *Stevia rebaudiana* indicates *S. rebaudiana* has significant potential for use as a natural antioxidant agent [122]. The DPPH activity of the extract (20, 40, 50, 100 and 200 μg/ml) was increased in a dose dependent manner, which was found in the range of 36.93–68.76% as compared to ascorbic acid 64.26–82.58%. The IC_{50} values of ethanolic extract and ascorbic acid in DPPH radical scavenging assay were obtained to be 93.46 and 26.75 μg/ml, respectively. The ethanolic extract was also found to scavenge the superoxide generated by EDTA/NBT system. Measurement of total phenolic content of the ethanolic extract of *S. rebaudiana* was achieved using Folin–Ciocalteau reagent containing 61.50 mg/g of phenolic content, which was found significantly higher when compared to reference standard gallic acid. The ethanolic extract also inhibited the hydroxyl radical, nitric oxide, superoxide anions with IC_{50} values of 93.46, 132.05 and 81.08 μg/ml, respectively.

Stevia Provides Immune System Support

Stevia leaf extracts exhibit significant antiviral and antimicrobial activity. For example, fermented aqueous extracts of stevia leaves have exhibited strong antimicrobial, antibacterial and antifungal activity towards a wide range of pathogenic bacteria, including enterohemorrhagic *Escherichia coli*, without affecting normal intestinal flora [123,124]. Hot water extracts of stevia leaf inhibit the replication of human rotavirus *in vitro* by blocking viral attachment to cells [125].

Several studies have demonstrated the inhibitory effects of stevia leaf extracts and their polyphenolic constituents on tumor promotion and initiation. Stevioside, the stevia leaf aglycones, steviol and isosteviol, and their metabolites have been reported to inhibit tumor promotion by blocking Epstein-Barr virus early antigen (EBV-EA) induction [126] as well as by reducing tumor formation in the two-stage mouse skin carcinogenesis model following sequential exposure to 7,12-dimethylbenz[a]anthracene (DMBA) and 12-*O*-tetradecanoylphorbol-13-acetate (TPA) [127-129]. The hydrolysis product of stevioside, isosteviol, potently inhibits DNA replication and human cancer cell growth *in vitro* (with LD_{50} values of 84 to 167 μMol) [130]. Isosteviol and the steviol glycosides, stevioside, rebaudioside A, rebaudioside C, and dulcoside A, also have been found to inhibit TPA-induced inflammation in mice [129,130]. These reports demonstrate that stevioside and its metabolites enhance mammalian immunosurveillance.

In a study investigating the immunomodulatory activity of stevioside by evaluating its effect on antibody titre, delayed type hypersensitivity response (DTH), macrophage phagocytosis, and B- and T-lymphocyte proliferation in mice found that stevioside administration stimulates these immune system functions [131]. Although not yet replicated in humans, together these *in vitro* and animal model studies suggest that stevia leaf extract is immunostimulatory.

Stevia as Treatment for Inflammatory Bowel Disease

Stevioside and steviol have been shown to exert anti-inflammatory effects on colonic epithelial cells [42]. Animal studies exhibit stevioside's inhibitory effect on intestinal smooth muscle contraction, stimulation of which is linked to hypermotility-associated diarrhea [132]. The effects of stevioside and its analogs, steviol, isosteviol, dihydroisosteviol, and isosteviol 16-oxime, on cAMP-regulated Cl secretion were studied in human T84 colonic epithelial cells and *in vivo* for their antidiarrheal efficacy [133]. Results indicated the major aglycone derivative, steviol, and its analogs, inhibited cAMP activated Cl secretion in intact T84 cells in a dose-dependent manner. The ineffectiveness of stevioside could be due to its molecular bulkiness, rendering it relatively impermeable to cell membranes, and thereby exhibiting a promising agent in antidiarrheal treatment.

STEVIA IS SAFE AND NON-TOXIC

The safety of stevia leaf extracts has been demonstrated repeatedly [134]. Stevia leaf extracts and their dominant bioactive components, stevioside and steviol, have been subjected to extensive genetic testing. Neither stevioside nor its aglycone steviol have been shown to react directly with DNA or demonstrate genotoxic damage in assays relevant to human risk [135]. Neither stevioside nor steviol produced clastogenic effects at extremely high intakes *in vivo* [135]. Stevioside was found to be nonmutagenic in mutagenicity tests using bacteria (reverse mutation assay, forward mutation assay, umu test and rec assay), cultured mammalian cells (chromosomal aberration test and gene mutation assay) and mice (micronucleus test) [136]. Steviol has not exhibited DNA-damaging activity in cultured animal cells and organs [137]. Stevioside has been without effects in acute and chronic toxicity studies in rats [138-140].

Another component of stevia leaves, rebaudioside A, also has been found to be nontoxic and nongenotoxic [141]. In addition, in a 4-week study, Wistar rats consuming up to 100,000 ppm of rebaudioside A daily exhibited no clinical, gross or histopathologic evidence of toxicity [142]. In a 13-week study, Wistar rats consuming up to 50,000 ppm of rebaudioside A exhibited no clinical, gross or histopathologic evidence of toxicity [142]. In a 90-day toxicity study, rats consuming up to 2,000 mg of rebaudioside A per kg of body weight daily was not associated with any signs of toxicity [143].

Furthermore, stevia leaf extracts and stevioside have produced no adverse effects on laboratory animal fertility, mating performance, pregnancy, number of fetuses, or growth and fertility of offspring [144-147]. Histopathological examination of the tissues of male rats at the ends of 28-and 90-day feeding studies revealed no macroscopic or microscopic changes in any reproductive organs following the cumulative consumption of up to 100,000 ppm of rebaudioside A [142,148]. In multigenerational studies, the daily consumption of up to 25,000 ppm of rebaudioside A was without effect on mating performance, fertility, gestation lengths, estrus cycles, or sperm motility, concentration or morphology in either the F_0 or F_1 generations [148,149]. From these data, a "no observed adverse effects level" (NOAEL) of between 2,048 and 2,273 mg of rebaudioside A per kg body weight per day was calculated [149]. Similar findings in multigenerational studies conducted on hamsters administered purified stevioside have confirmed the reproductive safety of purified steviol glycosides (and therefore of stevia leaf extracts) [150].

Pharmacokinetic analyses after single oral doses in healthy men report that purified rebaudioside A and stevioside and mixed steviosides undergo absorption and metabolism in humans with steviol glucuronide excreted primarily in the urine and steviol in the feces [151,152]. No safety concerns were noted as determined by reporting of adverse events, laboratory assessments of safety or vital signs [151,152].

Application of a Weight-of-Evidence approach to assess the genetic toxicology database produced the conclusion that the bioactive compounds in stevia leaf extract do not pose a risk of genetic damage in humans [135]. A review conducted by Central Queensland University and published in 2002 concluded that, "The safety of steviosides (as a general class of related compounds) for use in foods has been investigated through numerous studies and is well established" [44]. Taken together, the available data support the conclusion that the routine daily human consumption of 5 mg to 6 mg of stevia leaf extract as a dietary sweetener per kg of body weight is safe [148]. The inclusion of rebaudioside A in human foods is Generally Recognized As Safe (GRAS) [46].

DISCUSSION

Given its many health benefits, recent GRAS acceptance and existing evidence in support of stevia's safety for human consumption, little additional study is required to advance to

the next step: stevia as an approved sweetener for global use in human food products. The safety of stevia leaf extracts and their phytonutrient components sets the stage for high-quality randomized, double-blind, placebo-controlled human clinical trials that can confirm the effectiveness of stevia leaf extracts and their phytonutrient components in both general and specific disease-preventive and therapeutic settings.

STEVIA – A SAFE AND EFFECTIVE ALTERNATIVE TO SUCROSE AND FRUCTOSE

Given the negative health impacts of refined sucrose and high-fructose corn syrup on obesity and chronic human disease, consumers are ready for an effective and safe alternative. Not only are stevia leaf extracts and their phytonutrient components calorie-free, their consumption can promote health without threat of adverse reactions or toxic effects. As natural non-artificial sweeteners of food products, only long-lasting behavioral patterns, massive advertising budgets urging increased sucrose and fructose consumption, historically negative experience with some artificial sweeteners and cultural reluctance to embrace healthy practices that are currently outside of the marketing-driven mainstream prevent widespread replacement of sucrose and fructose with stevia and its component compounds.

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